Journal of Medical Ultrasound (2012) 20, 142—149

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REVIEW ARTICLE

A Review of Three-dimensional Ultrasound Applications in Fetal Growth Restriction

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Received 3 May, 2012; accepted 7 June, 2012

KEY WORDS
fetal growth restriction,
three-dimensional ultrasound

Fetal growth restriction (FGR), previously known as intrauterine growth restriction, remains one of the main challenges in maternity care. Three-dimensional ultrasound (3DUS) has the potential to provide improved visualization of the fetal anatomic morphology compared with conventional two-dimensional ultrasound imaging. The present paper reviews 3DUS studies in the diagnosis, evaluation and prediction of FGR, and discusses the possible clinical applications of 3DUS.

Introduction

Fetal growth restriction (FGR), previously known as intrauterine growth restriction, remains one of the main challenges in maternity care [1]. Normal fetal growth is a critical component of a healthy pregnancy and influences the long-term health of the offspring [1]. Fetal growth is regulated by many factors, including inherited genetic factors, also known as constitutional factors. Of note, FGR is defined as a fetus unable to reach its genetically determined growth potential in the contrary to constitutional small for gestational age (SGA) [2,3]. Customized standards for fetal growth and birth weight improve the detection of FGR by better distinction between physiological and pathological smallness and have led to internationally applicable norms. Such developments have resulted in new insights in the assessment of risk and surveillance during pregnancy [2].

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0929-6441
http://dx.doi.org/10.1016/j.jmu.2012.07.002

During the past two decades, three-dimensional ultrasound (3DUS) has evolved into a powerful technique [4,5]. In contrast to conventional two-dimensional US (2DUS) that only allow imaging of single planes, 3DUS offers several image displays that do not exist in 2DUS imaging. Thus, 3DUS offers a precise demonstration of the normal and abnormal anatomy of the fetus to the parents even in the absence of the patient. The digital storage of volumes permits virtual examinations by reloading of volumes and navigating through them, and especially benefits evaluation of fetal growth [5,6].

In the present review, we conducted a systematic review of the literature in the PubMed database related to the clinical applications of 3DUS for detecting, evaluating and predicting FGR. We sought to review 3DUS studies on the diagnosis, evaluation and prediction of FGR, and to make recommendations for the possible clinical applications of 3DUS.

Fetal growth restriction

The etiology of FGR is multifactorial, and can be further divided into maternal and fetal causes, and those resulting from uterine—placental vascular insufficiency; overlapping of etiological factors is not uncommon. Fetal factors include aneuploidy, genetic syndromes, and congenital infections. Common maternal factors include constitutional small, preeclampsia or hypertension, vasculopathy, cyanotic cardiopathies, restrictive pneumopathies, severe renal conditions, autoimmune diseases (e.g., collagenoses and antiphospholipid antibody syndrome), hereditary or acquired thrombophilia, hyperhomocysteinemia, and severe anemia are also associated with FGR.

Improvements have to start from a better definition of FGR, applying the concept of the fetal growth potential. To know the fetus is small *in utero* is the first step. Before the era of real-time ultrasound, serial fundal height measurement plotted on customized charts was a useful screening tool, whereas in modern times, fetal biometry and Doppler flowmetry are the mainstay for investigation and diagnosis of FGR [2,3,7].

Small for gestational age

Currently, estimated fetal weight or birth weight below the 10th percentile of certain reference points at a given gestational week is defined commonly as small for gestational age (SGA). The thresholds of fifth or third percentiles are also used [1]. A woman with a prior gestation complicated by FGR has nearly a 20% risk of recurrence [1,7,8]. Strategies to predict and prevent the recurrence are critical in obstetric management. Effective interventions for prevention of recurrent FGR include the following: a reproductive plan because spacing of pregnancies affects their outcome; optimization of maternal medical conditions; smoking cessation; accurate dating by first-trimester ultrasonography and monitoring of fetal growth with serial sonograms; and low-dose aspirin (80—160 mg) started before 20 weeks [9]. In women with nutritional deficiencies, optimizing caloric intake with low-protein ($<$ 25%) supplementation of 500—1000 calories may prevent recurrent FGR [2,3,7,8].

Failure to achieve genetic growth potential

The diagnostic elements of FGR are a fetus who is SGA and below the genetic potential. The growth potential is the driving force of fetal growth, whereas the placenta as the sole source of nutrients and oxygen might become the rate-limiting element of fetal growth if its function is impaired. Thus, placental dysfunction may prevent the fetus from reaching its full genetically determined growth potential. In this sense, fetal growth and its aberration provide an insight into placental function. Fetal growth is a proxy for the test of the effectiveness of the placenta, whose function is otherwise obscured during pregnancy [9].

3DUS: benefits versus conflicts

Traditionally, 3DUS volumes are obtained using the multiplanar and rotational techniques. The first involves sectioning the object into several planes separated by intervals established by the examiner. The outer surface of the object is traced on each slide, and at the end of the process, the equipment automatically displays the volume of the reconstructed object. The rotational technique [virtual organ computer-aided analysis (VOCAL)] involves the use of specific software (4D View; GE Healthcare, Kretztechnik, Zipf, Austria) and rotates the object around its own axis using a pre-established angle selected by the operator. The outer contours of consecutive planes displayed on the screen are manually traced to obtain area measurements. At the end of this process, the equipment automatically calculates the volume and reconstructs the selected object in a 3D format. All these formulas and software have been proved to be reliable, valid and reproducible [10—12].

Besides volumetric measurement, 3DUS assisted Doppler (3DPD) has also been proved to have potential to understand the association and the pathogenic mechanisms underlying FGR [13]. Before the era of 3DPD, Doppler ultrasound by 2D real-time ultrasound had been widely used for evaluating uteroplacental and fetoplacental perfusion [14]. For example, umbilical Doppler is a powerful tool in clinical practice, particularly in the diagnosis and management of SGA fetuses. Once a fetus has been diagnosed as SGA, normal uterine and umbilical flows suggest that it is small, but otherwise normal, whereas abnormal uterine/umbilical flows suggest that the growth disorder is due to an underlying defect in placental development, which is diagnostic of FGR [15].

Direct investigation of the perfusion of *in-vivo* placentas has become possible using 3DPD. Even very small blood movements within the investigated volume can be detected by a combination of power and color Doppler ultrasonography, and their impact in the given volume, representing the overall perfusion, is evaluated by indices computed by built-in algorithms [16]. 3D quantification of blood flow information in normal fetus from color Doppler has been obtained in normal fetus among normal fetus in [17—19].

Clinical applications of 3DUS in FGR

Multiple parameters measured by 3DUS have been studied for estimating fetal body weight, analyzing SGA symmetrically or not, and predicting FGR at later gestational age.

Fetal weight estimations for detecting SGA

The most common definition used equates FGR with a fetus that is less than the 10th percentile on a weight for gestational age curve (SGA fetus), although other percentiles (i.e., the fifth or third) have been used. In addition, there is significant controversy as to which growth curve should be used [20].

Fetal weight estimation by 3DUS

A number of 3DUS-based fetal weight references have been published since the late 1990s (Table 1) [21—27]. The volume of fetal thighs, arms and abdomen, single or in combination, were most often considered as the variables that correlated well with fetal weight [21—25]. These cross-sectional studies can provide a reference only for fetal size, and not fetal growth velocity. Even in first trimester, embryonic volume assessment can be accomplished by virtual reality techniques with 3DUS [27]. The measurement of limb volume and other soft tissue parameters has been achieved with the assistance of computer calculations and has been validated in different ethnic groups [23—25,27—30].

3DUS constructing normal fetal growth reference has been used to define normal and abnormal fetal growths. For the prenatal diagnosis of FGR, Chang et al have published a series of studies by analyzing testing threshold of the volume of femur, upper arms and humerus (Table 2) [31-33,38]. Using the 10th percentile as a cut-off value, these variables, especially the soft tissue of fetal upper arms, showed good accuracy (93.1% using fetal upper arm, 88.7% using humerus, and 91.3% using femur) [31—33].

Comparison of 2D and 3D in fetal birth weight estimation

For the past 30 years, the assessment of fetal size and growth has been essentially based on predictive models from 2D ultrasound measurements with the parameters of BPD (biperiatal diameters), AC (abdominal circumference) and FL (femur length). Since 3DUS imaging has allowed the accurate and reliable calculation of fetal organ volumes [28], some studies have shown that prediction of birth weight using fetal limb volumetry is more precise than with formulas using conventional 2DUS [31—33]. Some authors have debated that the proposed advantage of 3DUS is simply a result of the small phenotypic difference between the patients used to create these 3D formulas.

3DUS-assisting volume measurements of fetal organs

In FGR, reduction is more pronounced for hepatic volume than for head or upper abdominal circumference; hepatic volume is a better discriminator than head circumference but not upper abdominal circumference [28].

Fetal head/intracranial structures

Benavides et al have reported a case—control study that estimated differences in the volume measured by 3DUS of intracranial structures (total intracranial, frontal area, cerebellar and thalamic volumes) between 39 FGR fetuses and 39 matched appropriate for gestational age (AGA) fetuses. FGR fetuses showed differences in the volume of all intracranial structures, except the thalamus, compared with AGA fetuses, with the largest difference found in the frontal region [34].

Fetal abdomen

Measurement of the fetal abdominal circumference is the most sensitive predictor in the fetal weight estimation formulae using real-time 2DUS parameters [35]. A good correlation has been found between abdominal circumference and length of the right lobe of the liver [36,37].

Fetal limbs

Lee et al have used 3DUS to calculate fractional limb volumes in the third trimester and have developed a formula incorporating fractional thigh volume and AC that gives a slight but statistically significant improvement in fetal weight estimation compared with traditional 2DUS techniques [24]. The 3DUS-assisted measurement of volume of fetal limbs, single or in combination, has been reported as a good predicting variable of FGR in the series reported by Chang et al [23,31,32,38]. The reported positive predictive value of the soft tissue of fetal femur is reported to be as high as 99%.

Placenta

Wolf et al have reported the second-trimester placental volume measurement using a modification of the rectangular formula by means of conventional 2DUS [38]. The introduction of 3DUS could facilitate the novel assessment of the placenta, such as surface-rendered imaging and volume measurement [39]. However, studies on the prediction of adverse pregnancy outcomes, including FGR and pre-eclampsia, using the placental volume measurement in the first trimester of pregnancy have shown inconsistent results [39].

3DUS assisting Doppler measurement of blood flow analysis

The potential value of 3DPD indices is the calculation of blood perfusion in a volume of tissue, offering a more complete perspective of regional hemodynamic changes. 3D Doppler ultrasound can observe intraplacental vessel characteristics such as the density of vessels, branches, caliber measurements and tortuosity of either the placental or uterine vessels [40]. 3DPD was found to be

Table 1 Studies of fetal weight estimation by 3DUS.

Studies	Year	Subjects (n)	Used variables	Correlation	Error	Ref.
Brinkley et al	1984	Live fetuses within 48 h prior to delivery (41)	19 measured variables	0.93	73 g/kg	[29]
Lee et al	1997	Term fetuses (18)	Abdominal and thigh volumes	N.A.	17 fetuses within 10% of true values	[24]
Chang et al	1997	Fetuses delivered within 48 h after ultrasound examination (100)	Thigh volume	$r = 0.89$	Mean percent error (1.5%),	[23]
Liang et al	1997	Fetuses delivered within 48 h after ultrasound examination (105)	Upper arm volume	$r = 0.92$	Mean percentage error (0.53%)	[25]
Schild et al	2000	Caucasians with a singleton pregnancy delivered within 7 d after ultrasound scanning (135)	Upper thigh volume; arm volume; abdominal volume	0.903–0.973	Mean absolute percentage error ($6 \pm 5\%$)	[21]
Schild et al	2008	Singleton fetuses weighing $\leq$1.6 kg at birth obtained by 2DUS and 3DUS examination within 1 wk before delivery (150)	Femur length, biparietal diameter; abdominal volume by 3DUS, head circumference, thigh volume by 3DUS	N.A.	Mean percentage error ($0.66 \pm 9.55\%$)	[22]
Lindell et al	2009	Pregnant women in whom the fetus weight estimation was performed at $\geq$287 d of gestation within 4 d of delivery (176)	Fetal head, abdomen and femur using 2DUS, and fetal thigh volume using 3DUS.	0.67–0.71 (depending on the formula)	Mean percentage error ($7.0 \pm 6.3\%$)	[27]

2DUS = two-dimensional ultrasound; 3DUS = three-dimensional ultrasound; N.A. = not available.

Table 2 Studies reporting FGR prediction using 3DUS.

Study	Year	Used variable	Study subjects	Sensitivity	Specificity	Accuracy	Ref.
Chang et al	2005	10th percentile by upper arm volume	40 fetuses with FGR and 442 fetuses without FGR	97.5%	92.8%	93.1%.	[31]
Chang et al	2006	10th percentile of fetal humerus volume	42 fetuses with FGR and 258 fetuses without FGR	97.6%,	87.2%	88.7%.	[32]
Chang et al	2007	10th percentile of fetal femur volume	42 fetuses with FGR and 304 fetuses without FGR	71.4%,	94.1%,	91.3%.	[33]
Chang et al	2011	5th percentile of soft tissue volume of fetal upper arm	219 AGA fetuses and 44 SGA fetuses	84.1%	93.4%	91.9%	[38]

3DUS = three-dimensional ultrasound; AGA = average for gestational age; FGR = fetal growth restriction; SGA = small for gestational age.

superior to 2D power Doppler ultrasound for the detection of secondary and tertiary stem vessels in the placenta. Todros has found that the different approaches (morphometric, morphological, mathematical, immunohistochemical and molecular) have contributed to elucidation of which anomalies of the vascular villous tree underlie Doppler findings. 3DUS may be useful in the study of feto-placental perfusion. However, the unsolved question is why developmental villous tree anomalies occur [41]. Liver, kidney and brain have been studied showing increasing blood flow patterns as gestation progresses [17–19].

Three perfusion indices based on the voxel information of the power Doppler ultrasound signals can be calculated within the rendered volume: the vascular index (VI, percentage of voxels in the volume); flow index (FI, mean voxel intensity in the volume); and vascular/flow index. Several reports on the fetal brain using 3DPD perfusion indices have been published, confirming the increment in brain blood flow perfusion in FGR fetuses [42].

Placental vasculature

3DPD can provide new insights into placental pathophysiology [40]. 3DPD indices [vascularization index (VI), vascularization flow index (VFI) and FI] are reported to be correlated with placental perfusion. Among them FI appears to be the most reliable index because of its low intraplacental variability and identifies the most severe cases of placental impairment [16]. Yigiter et al to investigate correlations between first trimester placental volume and blood flow indexes, bilateral uterine artery pulsatility indexes, notching, and biochemical parameters: pregnancy-associated plasma protein-A (PAPP-A), free β-human chorionic gonadotropin, and insulin-like growth factor-1 to predict the high-risk pregnancies in the first trimester. The result showed significant correlations between placental volume and biochemical parameters, and [43].

Uterine vessels

In high-risk women, uterine artery Doppler waveform analysis performs best in the prediction of severe adverse outcomes, and is better than clinical risk assessment in the prediction of pre-eclampsia and SGA babies [44,45]. Abnormal uterine artery waveforms are a better predictor of pre-eclampsia than of FGR. A pulsatility index, alone or combined with notching, was the most predictive Doppler index in a meta-analysis [44,46]. Gigano et al have tested the hemodynamic changes in uterine vessels, measured with Doppler ultrasound supported by 3D angioimaging, in the second and third trimester of pregnancy. In this pilot study, mean uterine artery diameter and blood flow velocity increased significantly ($p < 0.0001$) from mid-gestation to late gestation from 2.6 mm and 67.5 cm/s, to 3.0 mm and 85.3 cm/s, respectively, yielding an increasing absolute flow throughout gestation [47]. 3DPD is a useful and effective method for assessing endometrial blood flow in IUI cycles and *in vitro* fertilization cycles, and good endometrial blood flow is associated with pregnancy [48,49]. However, there is limited evidence for the association between FGR and 3DPD-detected poor endometrial blood flow or high-resistance uterine arteries.

Umbilical vessels

Velamentous insertion of the umbilical cord has been associated with several obstetric complications including FGR. The role of 3DUS in evaluating the placental cord insertion site is no more satisfactory that the combination of gray-scale ultrasound and color Doppler ultrasound [50].

FGR prediction

Serial prenatal ultrasound for estimating fetal weight has been proposed to monitor the occurrence of FGR. Indeed, estimated fetal weight is commonly used as an index of fetal growth, although in some clinical settings, it is of limited value to prevent FGR if no adequate parameters to predict the condition happen in the future. Multidisciplinary treatments have been proposed and validated to improve the outcome by reducing the overall incidence of complications associated with uteroplacental insufficiency in high-risk mothers, either with antiphospholipid syndrome or pre-eclampsia [51,52].

Volume of fetal organs

Due to fetal malnutrition, reduction in fetal hepatic weight is more pronounced than is reduction in brain weight because of the brain-sparing effect, which reflects redistribution of fetal blood flow during chronic fetal hypoxemia [38]. Measurement of fetal hepatic volume may thus contribute to the early detection of FGR. The decrease in hepatic volume is more pronounced among fetuses with body weight lower than average, below the 50th percentile, than is the reduction in head circumference or upper abdominal circumference [27].

Fetal liver

In fetal growth restriction, reduction is more pronounced for hepatic volume than for head or upper abdominal circumference; hepatic volume is a better discriminator than head circumference but not upper abdominal circumference [27].

Fetal brain

Prenatal assessment of the fetal head/brain is usually performed using 2DUS biometric measurements. Benavides-Serralde et al have studied the intracranial volume measured by 3DUS in FGR and normal fetuses [34]. Volumes were satisfactorily obtained in all fetuses. All net volumes except those for the thalamus were significantly smaller in FGR fetuses. After adjusting volumes for biparietal diameter, the frontal volume was significantly smaller and the thalamic volume significantly greater in FGR fetuses than in fetuses with normal growth. Significant intergroup differences in the ratios between structures were found only in those involving the frontal region. The cerebellum diameter itself is correlated well with gestational age and also the cerebellar volume measured by 3DUS. FGR fetuses show differences in the volume of intracranial structures compared with AGA fetuses, with the largest difference found in the frontal region. However, interobserver and intraobserver intraclass correlation coefficients were only 0.66 (95% confidence interval, 0.42—0.79) while measuring the frontal region.

Volume/vasculature of placenta measured by 3DUS

Although placental growth in the second trimester is too heterogeneous to justify using this method as a clinical tool, it can provide new information on placental physiology underlying unfavorable obstetric outcomes [40]. 3DPD angiography has been largely used for the subjective assessment of vascular patterns. With the recent advances in 3DPD ultrasound as well as quantitative 3DPD histogram analysis, quantitative and qualitative assessments of the vascularization and blood flow of the placenta have become feasible [39]. Rizo et al have reported a study investigating the first-trimester placental volume and 3DPD vascularization of pregnancies with low serum PAPP-A levels, and have related these findings to outcomes of 87 pregnancies. These indices were significantly lower in the 11 pregnancies with birth weights below the 10th percentile and abnormal umbilical Doppler findings later in gestation. Placental vascular indices were significantly related to the severity of FGR but not to the levels of PAPP-A and placental volumes [41]. Recently, Pomorski et al have conducted a prospective study on a group of 100 normal and 20 FGR pregnancies between 22 and 42 weeks of gestation. The results showed that quantitative assessment of placental vasculature and volume by means of 3DPD and VOCAL technique is an adjunctive modality for differentiation between normal and FGR pregnancies [14]. All the fetal cerebral 3D vascular indices, VI, FI and VFI, are increased in FGR [42]. In these fetuses, there were more cases suggesting hemodynamic redistribution than expected by conventional Doppler studies. Morel et al have conducted an *in vivo* study confirming a significant correlation between true blood perfusion and quantitative 3D Doppler indices measured within the uteroplacental unit in sheep [53].

Conclusion

3DUS has the potential to provide improved visualization of the fetal anatomic morphology compared with conventional 2DUS. Although no preferred method for 3DUS estimation of fetal weight has emerged from this review, the advent of 3DUS imaging has allowed the accurate and reliable calculation of fetal organ and soft tissue volumes. As reported by recent studies, prediction of birth weight using fetal limbs or liver is more precise than that obtained using conventional 2DUS parameters.

Acknowledgments

Special thanks to all the staff of the Prenatal Ultrasound Laboratory, Department of Obstetrics and Gynecology, National Cheng Kung University Hospital and College of Medicine, for their assistance with this manuscript.

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